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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/557,907	HORTON ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5-3-06, 5-8-06 and 5-22-06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,16-18,30-35,38-41,43,46-50,66,69,71-74,77,78 and 83-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7,16-18,30-35,38-41,43,46-50,66,69,71-74,77,78 and 83-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's request filed on 5-8-06 has been entered.

The amendment filed in the response of 5-3-06 was not entered because it was non-responsive.

The amendment filed 5-22-06 has been entered. It is assumed that the arguments filed 5-3-06 apply to the claims in the amendment filed 5-22-06.

Applicant's arguments filed 5-3-06 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3-7, 16-18, 30-35, 38-41, 43, 46-50, 66, 69, 71-74, 77, 78 and 83-86 remain pending and under consideration in the instant office action.

Claim Rejections - 35 USC § 112

The rejection of claims 1, 3-7, 16-18, 30-35, 38-41, 43, 46-50, 66, 69, 71-74, 77, 78 and 83-86 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention has been withdrawn. Specifically, the rejection regarding the phrase "mammal in need of cancer treatment" in claim 1, 66 and 78 has been withdrawn because the phrase has been deleted.

However, claims 1, 3-7, 16-18, 30-35, 38-41, 43 and 46-50 are newly rejected as amended under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The genus of "administering into a non-injured muscle of a mammal" as claimed in claim 1 as amended is new matter. Applicants point to pg 11, lines 1-9, and pg 104, lines 9-22.

Pg 11, lines 1-9, teach:

> "Many of these attempts to enhance tissue transduction have used agents that destroy muscle (bupivacaine, barium chloride) and actually lower expression (Norman, J. et al., Methods in Molec. Med. 29: 185-196 (1999)); have to be pre-injected before the DNA (sucrose; are expensive organic polymers (polyvinyl pyrollidine), mutagens (intercalaters), antigenic proteins (histones) or devices that destroy muscle tissue (needless or needle-free injectors; or need to be inserted surgically (sutures, sponges, intravascular pressure). Furthermore, most of these methods may be expensive and not suitable or practical for human use."

Pg 104, lines 9-22, teach:

> "As shown in FIGs. 3-5 and FIG. 7A, mice bearing different tumors were found to significantly benefit from intramuscular injection of different cytokines. To test the

> efficacy of IFNα plasmid, C57BL/6 mice bearing subcutaneous B l 6F10 melanoma, subcutaneous glioma 261, or intradermal 545076 tumors, or DBA/2 mice bearing subcutaneous Cloudman melanoma were injected with 100 pg either of VR41 1 l (mIFNa) or VR1055 (control), twice per week for three weeks, beginning on day 4 after tumor cell injection (n = 8-1 0 mice per group). In all three subcutaneous tumor models, the mice treated intramuscularly with VR4 l l 1 had a significant reduction in tumor volume ($p<0.05$) (FIGs. 3A, 3C, and 3E), and a significant enhancement of survival ($p<0.02$) compared to the mice that received the control plasmid (FIGs. 3B, 3D, and 3F). In the intradermal tumor model, mice treated with intramuscular VR4l 1 1 had a significant reduction in primary tumor volume ($p<0.00l$) compared to the mice that received the control plasmid (FIG. 7A)."

It is not readily apparent applicants contemplated the breadth of administering into any "non-injured muscle" as broadly claimed. First, it cannot be determined if applicants are saying all of the techniques discussed on pg 11, lines 1-9, are examples of administering into injured muscle or whether only those that "destroy muscle (bupivacaine, barium chloride)" or "destroy muscle tissue (needless or needle-free injectors) injure muscle. Second, it cannot be determined whether administering a plasmid surgically (line 7-8) is "administering into a non-injured muscle" or not. Third, muscle tissue that is not "destroyed" as discussed twice on pg 11, lines 1-9, does not have the same scope as non-injured muscle as claimed. Fourth, muscle tissue that is injured by intramuscular injection in the absence of any of the techniques on pg 11, lines 1-9, may be considered injured muscle because an inflammatory response would occur. Fifth, intramuscular injection using needless injectors could destroy muscle tissue and still be "administering into a non-injured muscle of a mammal" as claimed because the muscle is non-injured upon needless injection. Accordingly, the

specification as originally filed did not contemplate the genus of "non-injured muscle" as claimed.

The rejections of claims 1, 3-7, 16-18, 30-35, 38-41, 43, 46-50, 66, 69, 71-74, 77, 78 and 83-86 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention have been withdrawn.

The rejection regarding the phrase "mammal in need of cancer treatment" in claims 1, 66 and 78 has been withdrawn because the phrase has been deleted.

The rejection of claim 1 regarding whether the phrase "said cancer" in the last line refers to the phrase "treating cancer" or the phrase "in need of cancer treatment" has been withdrawn in view of the amendment.

The rejection of claim 1 regarding the nexus between cancer and treatment has been withdrawn in view of the amendment.

The rejection of claims 4-6 and 30-34 regarding the type of "cancer" in claim 1 has been withdrawn in view of the amendment.

The rejection of claim 66 and 78 regarding the nexus of the claims has been withdrawn in view of the amendment.

The rejection regarding the phrase "said mammal in need of cancer treatment" in claims 66 and 78 lacking antecedent basis has been withdrawn in view of the amendment.

Claim Rejections - 35 USC § 102

Claims 1, 3, 7, 35, 38 and 43 remain rejected under 35 U.S.C. 102(a) as being anticipated by Lawson (J. Interferon and Cytokine Res., May 1997, Vol. 17, pg 255-261) for reasons of record.

Lawson injected plasmid DNA encoding IFN-α operably linked to the human β actin promoter or the CMVIE promoter in saline into the skeletal tibialis anterior muscle of mice. The injection was performed on crush injured, bupivacain injured and normal muscle (Table 2 and Table 4). While the injection technique in crush or bupivacain injured muscle resulted in physiologically significant amounts of IFN-α in the systemic circulation (pg 256, Fig. 1B; pg 257, col. 1, "Injection of DNA constructs"; "Circulating IFN protein levels in serum"; Table 4 (22 and 36 and ≤3.9 IU/ml); see also the specification on pg 4, lines 24-26), the injection technique in normal muscle also resulted in ≤3.9 IU/ml IFN-α in the serum. Without evidence to the contrary, ≤3.9 IU/ml IFN-α in the serum (pg 259, Table 4, "normal muscle) is inherently "an amount effective to treat said cancer" as claimed.

The last two sentences of Lawson state: "[t]he surprisingly simple technique of gene transfer via intramuscular injection of naked DNA allows further investigation of the relative in vivo efficacies of the functional capabilities of each type I IFN subtype in animal models. We are currently systematically analyzing antitumor and antiviral actions of the murine IFNs in established animal models of disease." It is readily apparent from the last two sentences that Lawson applied the method of administering naked plasmid DNA encoding IFNs intramuscularly to established tumor models, i.e.

mammals having tumors, which is equivalent to "a mammal with cancer" in the body of claim 1. Therefore, Lawson teaches administering to "a mammal with cancer" as claimed.

The INF-α gene (pg 256, Fig. A) described by Lawson inherently had a polyA and transcription termination signal as claimed (3) because the plasmid expressed biologically active IFN-α (pg 256, col. 2, lines 4-5).

The body of claim 1 does not require a positive clear step of inhibiting tumor growth.

Dependent claims 4-6 and 30-34 have been excluded because the claims limit the type of "cancer" in claim 1 to specific types of cancer; however, the last two sentences of Lawson do not teach the type of cancer models used.

Applicants argue Lawson only detected serum levels of IFN-α in the animals that underwent crush injury. Applicants' argument is not persuasive. Lawson taught injecting plasmid into normal muscle and obtaining ≤3.9 IU/ml IFN-α in the serum (pg 259, Table 4, "normal muscle). Without evidence to the contrary, ≤3.9 IU/ml IFN-α in the serum is inherently "an amount effective to treat said cancer" as claimed.

Applicants argue Lawson did not administer the plasmid to animals having cancer as claimed. Applicants' argument is not persuasive. The last two sentences of Lawson state: "[t]he surprisingly simple technique of gene transfer via intramuscular injection of naked DNA allows further investigation of the relative in vivo efficacies of the functional capabilities of each type I IFN subtype in animal models. We are currently systematically analyzing antitumor and antiviral actions of the murine IFNs in

established animal models of disease." It is readily apparent from the last two sentences that Lawson applied the method of administering naked plasmid DNA encoding IFNs intramuscularly to established tumor models, i.e. mammals having tumors, which is equivalent to "a mammal with cancer" in the body of claim 1. Therefore, Lawson teaches administering the plasmid to "a mammal with cancer" as claimed.

Claim Rejections - 35 USC § 103

Claims 1, 3, 4, 7, 30, 31, 35, 38, 43 and 46-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawson (J. Interferon and Cytokine Res., May 1997, Vol. 17, pg 255-261) in view of Zhang of record (PNAS, April 1996, Vol. 93, pg 4513-4518).

Lawson injected plasmid DNA encoding IFN-α operably linked to the human β actin promoter or the CMVIE promoter in saline into the skeletal tibialis anterior muscle of mice. The injection was performed on crush injured, bupivacain injured and normal muscle (Table 2 and Table 4). While the injection technique in crush or bupivacain injured muscle resulted in physiologically significant amounts of IFN-α in the systemic circulation (pg 256, Fig. 1B; pg 257, col. 1, "Injection of DNA constructs"; "Circulating IFN protein levels in serum"; Table 4 (22 and 36 and ≤3.9 IU/ml); see also the specification on pg 4, lines 24-26), the injection technique in normal muscle also resulted in IFN-α in the serum. Without evidence to the contrary, ≤3.9 IU/ml IFN-α in the serum as taught by Lawson (pg 259, Table 4, "normal muscle) is inherently "an amount

effective to treat said cancer" as claimed. The INF-α gene (pg 256, Fig. A) described by Lawson inherently had a polyA and transcription termination signal as claimed (3) because the plasmid expressed biologically active IFN-α (pg 256, col. 2, lines 4-5). Lawson did not inject a non-injured muscle of a mammal with breast or melanoma cancer as claimed.

However, Zhang established breast or melanoma tumors in the breast or thigh of mice then injected adenoviral particles encoding INF into the mice three times resulting in tumor regression.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to inject a plasmid encoding INF-α into the muscle of a mouse as taught by Lawson, wherein the mouse had an established breast or melanoma tumor as described by Zhang. One or ordinary skill in the art at the time the invention was made would have been motivated to use the technique described by Lawson in the mice with tumors described by Zhang because Lawson suggested using the technique in disease models (pg 256, col. 1, lines 12-14), specifically tumor models (pg 260, col. 2, last sentence).

It also would have been obvious to one of ordinary skill in the art at the time the invention was made to inject a vector encoding INF into a mouse with a tumor three times as taught by Zhang, wherein the vector was a plasmid encoding INF-α and was injected intramuscularly as described by Zhang. One or ordinary skill in the art at the time the invention was made would have been motivated to replace the viral vector encoding IFN-consensus of Zhang with the plasmid encoding IFN-α described by

Lawson to avoid the pathogenicity of adenoviruses (pg 4513, col. 1, last line, of Zhang) and because Lawson suggested using the plasmid in disease models (pg 256, col. 1, lines 12-14), specifically tumor models (pg 260, col. 2, last sentence).

One of ordinary skill in the art at the time of filing would have had a reasonable expectation of successfully treating tumors in the mice described by Zhang using the technique of Lawson because the serum level of IFN-α in "normal muscle" described by Lawson (≤3.9 IU/ml) is capable of treating cancer (see pg 259, Table 4). The serum levels described by Lawson indicate systemic delivery of INF-α, which would ultimately allow contact of INF-α with the tumor through the vasculature.

Claims 46-49 are included because injecting the vector three times as taught by Zhang is equivalent to injecting the plasmid before, during or after gene therapy, i.e. the first injection is followed by gene therapy (the second and third injections), the second injection is preceded and followed by gene therapy (the first and third injection, etc.)

Applicants' arguments regarding Lawson are discussed above under the 102 rejection.

Applicants summarize the teachings of Lawson and Zhang and argue all the limitations are not met by the combined teachings of Lawson taken with Zhang. Applicants' argument is not persuasive. Lawson meets all the limitations of claim 1. Zhang has been used to meet the specific types of cancer listed in claim 4, et al., i.e. breast and melanoma tumor models. The combined teachings of Lawson and Zhang meet all the limitations claimed. Applicants' summary of Zhang is incomplete. Zhang taught intramuscular injection of a vector encoding IFN-α into mice having breast or

melanoma tumors treated the tumors. Applicants have not pointed to one specific element that the combined teachings of Lawson and Zhang fail to teach.

Applicants argue that one of ordinary skill would not have been motivated to combine Lawson and Zhang because Lawson taught away from Zhang. Applicants assert Lawson teaches that only crush-injured muscle mice developed a systemic IFN-α response in tumor bearing mammals upon intramuscular injection. Applicants argue that one of skill would not have been motivated to cause a crush injury in order to treat cancer. Applicants' arguments are not persuasive. The teachings of Lawson are not limited to crush-injured muscle. Without evidence to the contrary, ≤3.9 IU/ml IFN-α in the serum (pg 259, Table 4, "normal muscle) is inherently "an amount effective to treat said cancer" as claimed. Furthermore, Lawson specifically suggested administration of naked plasmid encoding IFNs via intramuscular injection to established tumor models (last two sentences of Lawson).

Claims 1, 3, 7, 35, 38 and 43 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ogura (Cancer research, 1990 Aug 15, Vol. 50 (16) pg 5102-6) in view of Lawson (J. Interferon and Cytokine Res., May 1997, Vol. 17, pg 255-261).

Ogura established tumors in mice then injected a chamber apparatus subcutaneously, wherein the chamber apparatus comprised fibroblasts transfected with a plasmid encoding INF-α into the tumors resulting in tumor regression (pg 5103, last full ¶). The tumors were made using the chronic myelocytic leukemia cell line, KU812

(pg 5102, last 4 lines). Ogura did not inject the vector intramuscularly into a non-injured muscle in the absence of the fibroblasts.

However, Lawson injected plasmid DNA encoding IFN-α operably linked to the human β actin promoter or the CMVIE promoter in saline into the skeletal tibialis anterior muscle of mice. The injection was performed on crush injured, bupivacain injured and normal muscle (Table 2 and Table 4). While the injection technique in crush or bupivacain injured muscle resulted in physiologically significant amounts of IFN-α in the systemic circulation (pg 256, Fig. 1B; pg 257, col. 1, "Injection of DNA constructs"; "Circulating IFN protein levels in serum"; Table 4 (22 and 36 and ≤3.9 IU/ml); see also the specification on pg 4, lines 24-26), the injection technique in normal muscle also resulted in IFN-α in the serum. Without evidence to the contrary, ≤3.9 IU/ml IFN-α in the serum as taught by Lawson (pg 259, Table 4, "normal muscle) is inherently "an amount effective to treat said cancer" as claimed. The INF-α gene (pg 256, Fig. A) described by Lawson inherently had a polyA and transcription termination signal as claimed (3) because the plasmid expressed biologically active IFN-α (pg 256, col. 2, lines 4-5).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to inject a plasmid encoding INF-α into the mouse with a tumor as taught by Ogura, wherein the plasmid was in the absence of cells and injected intramuscularly into non-injured muscle as described by Lawson. One or ordinary skill in the art at the time the invention was made would have been motivated to replace the cells transfected with a plasmid encoding IFN-α described by Ogura with plasmids

encoding IFN-α described by Lawson to avoid the steps of transfecting cells with the plasmid and culturing the cells in vitro.

It also would have been obvious to one of ordinary skill in the art at the time the invention was made to inject a plasmid encoding INF-α into a mouse intramuscularly into non-injured muscle as taught by Lawson, wherein the mice had established myelocytic leukemia tumors as described by Ogura. One or ordinary skill in the art at the time the invention was made would have been motivated to perform the technique of Lawson in the mice described by Ogura because Lawson suggested using the plasmid in disease models (pg 256, col. 1, lines 12-14), specifically tumor models (pg 260, col. 2, last sentence).

One of ordinary skill in the art at the time of filing would have had a reasonable expectation of successfully treating tumors in the mice described by Ogura using the technique of Lawson because without evidence to the contrary, ≤3.9 IU/ml IFN-α in the serum as taught by Lawson (pg 259, Table 4, "normal muscle) is inherently "an amount effective to treat said cancer" as claimed. The serum level indicates systemic delivery of INF-α, which would ultimately allow contact of INF-α with the tumor through the vasculature.

Applicants' summary of the rejection on pg 14, last three lines, is incorrect. The rejection is based on Ogura in view of Lawson, not Lawson in view of Ogura.

Applicants' arguments regarding Lawson are discussed above under the 102 rejection.

Applicants summarize the teachings of Ogura and Lawson and argue all the limitations are not met by the combined teachings of Ogura taken with Lawson. Applicants' argument is not persuasive. Both Ogura and Lawson taught performing their techniques in mammals having cancer as claimed. The teachings of Lawson are not limited to injecting plasmid into a crush-injured muscle. Applicants have not pointed to one specific element that the combined teachings of Lawson and Zhang fail to teach.

Applicants argue that one of ordinary skill would not have been motivated to combine Ogura and Lawson because Lawson taught away from Ogura. Applicants assert Lawson teaches that only crush-injured muscle mice developed a systemic IFN-α response in tumor bearing mammals upon intramuscular injection. Applicants' arguments are not persuasive. The teachings of Lawson are not limited to obtaining IFN-α serum expression in crush-injured muscle. Without evidence to the contrary, obtaining ≤3.9 IU/ml IFN-α in the serum after injecting "normal muscle" (pg 259, Table 4, "normal muscle) is inherently "an amount effective to treat said cancer" as claimed. Furthermore, Lawson specifically suggested administration of naked plasmid encoding IFNs via intramuscular injection to established tumor models (last two sentences of Lawson). Ogura is one such tumor model.

Claims 66, 69, 71-73 78 and 83-85 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Aoki (Human gene therapy, 1997 Jun 10, Vol. 8 (9) pg 1105-13) in view of Lawson (J. Interferon and Cytokine Res., May 1997, Vol. 17, pg 255-261) and Welander (Investigational New drugs, 1987, Vol. 5, Suppl, S47-59, abstract only).

Aoki established pancreatic tumors in the peritoneal cavity of mice then injected a plasmid encoding HSV-TK operably linked to a promoter in a cationic liposome into the peritoneal cavity of the mice resulting in tumor regression. Aoki did not inject a vector encoding IFN-α.

However, Lawson injected plasmid DNA encoding IFN-α operably linked to the human β actin promoter or the CMVIE promoter in saline into the skeletal tibialis anterior muscle of mice. The injection was performed on crush injured, bupivacain injured and normal muscle (Table 2 and Table 4). While the injection technique in crush or bupivacain injured muscle resulted in physiologically significant amounts of IFN-α in the systemic circulation (pg 256, Fig. 1B; pg 257, col. 1, "Injection of DNA constructs"; "Circulating IFN protein levels in serum"; Table 4 (22 and 36 and ≤3.9 IU/ml); see also the specification on pg 4, lines 24-26), the injection technique in normal muscle also resulted in IFN-α in the serum. Without evidence to the contrary, ≤3.9 IU/ml IFN-α in the serum as taught by Lawson (pg 259, Table 4, "normal muscle) is inherently "an amount effective to treat said cancer" as claimed. The INF-α gene (pg 256, Fig. A) described by Lawson inherently had a polyA and transcription termination signal as claimed (3) because the plasmid expressed biologically active IFN-α (pg 256, col. 2, lines 4-5).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to inject a plasmid encoding a protein capable of treating cancer in a cationic liposome into the peritoneal cavity of a mouse with a peritoneal tumor as taught by Aoki, wherein the plasmid encoded IFN-α as described by Lawson. One or ordinary skill in the art at the time the invention was made would have been motivated

to replace the plasmid encoding HSV-TK described by Aoki with the plasmid encoding IFN-α described by Lawson to avoid the use of the suicide gene HSV-TK and because intraperitoneal injection of INF-α was known to have anti-tumor effect (Welander abstract, last 5 lines).

It also would have been obvious to one of ordinary skill in the art at the time the invention was made to inject a plasmid encoding INF-α into a mouse as taught by Lawson, wherein the mice had established tumors as described by Aoki. One or ordinary skill in the art at the time the invention was made would have been motivated to inject plasmid into mice as taught by Lawson having established peritoneal tumors as described by Aoki because Lawson suggested using the plasmid in established disease models (pg 256, col. 1, lines 12-14), specifically tumor models (pg 260, col. 2, last sentence). One of ordinary skill would have been motivated to inject the plasmid encoding INF-α described by Lawson intraperitoneally as described by Aoki to maximize the level of INF-α and the tumor cell exposure to INF-α as described by Welander.

Applicants' arguments summarize the teachings of Aoki, Lawson and Welander (pg 13, last 8 lines) and conclude that the combined teachings of Aoki, Lawson and Welander do not teach all the limitations of claims. Applicants' argument is not persuasive because applicants have not pointed to one specific element that the combined teachings of Aoki, Lawson and Welander fail to teach.

Applicants argue that one of ordinary skill would not have been motivated to combine Aoki, Lawson and Welander because Lawson taught away from the combination. Applicants assert that one of skill would not have been motivated to cause

a crush injury as taught by Lawson in order to treat cancer as taught by Aoki. Applicants argue Lawson teaches away from the claimed invention because Lawson taught only crush-injured mice developed a systemic IFN-α response. Applicants' arguments are not persuasive. The teachings of Lawson are not limited to injecting crush-injured muscle. Without evidence to the contrary, injecting non-injured muscle and obtaining ≤3.9 IU/ml IFN-α in the serum (pg 259, Table 4, "normal muscle) is equivalent to "administering into a non-injured muscle" and obtaining IFN-α expression "in an amount effective to treat said cancer" as claimed. Lawson specifically suggested administration of naked plasmid encoding IFNs into established tumor models (last two sentences of Lawson). Lawson does not teach away from injecting a plasmid in a cationic liposome into the peritoneal cavity as taught by Aoki.

Claims 1, 3-7, 30-35, 39-41, 43 and 46-49 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Okamoto (Gene Therapy, 1997, Vol. 4, pg 969-976) in view of Lawson (J. Interferon and Cytokine Res., May 1997, Vol. 17, pg 255-261).

Okamoto injected a plasmid encoding a protein operably linked to a promoter in a cationic liposome into the quadricep of mice (Fig. 1). The mice were immunized three times (pg 971, Fig. 2 caption). Okamoto did not inject a vector encoding IFN-α into mice having cancer.

However, Lawson injected plasmid DNA encoding IFN-α operably linked to the human β actin promoter or the CMVIE promoter in saline into the skeletal tibialis anterior muscle of mice. The injection was performed on crush injured, bupivacain

injured and normal muscle (Table 2 and Table 4). While the injection technique in crush or bupivacain injured muscle resulted in physiologically significant amounts of IFN-α in the systemic circulation (pg 256, Fig. 1B; pg 257, col. 1, "Injection of DNA constructs"; "Circulating IFN protein levels in serum"; Table 4 (22 and 36 and ≤3.9 IU/ml); see also the specification on pg 4, lines 24-26), the injection technique in normal muscle also resulted in IFN-α in the serum. Without evidence to the contrary, ≤3.9 IU/ml IFN-α in the serum as taught by Lawson (pg 259, Table 4, "normal muscle) is inherently "an amount effective to treat said cancer" as claimed. The INF-α gene (pg 256, Fig. A) described by Lawson inherently had a polyA and transcription termination signal as claimed (3) because the plasmid expressed biologically active IFN-α (pg 256, col. 2, lines 4-5).

The last two sentences of Lawson state: "[t]he surprisingly simple technique of gene transfer via intramuscular injection of naked DNA allows further investigation of the relative in vivo efficacies of the functional capabilities of each type I IFN subtype in animal models. We are currently systematically analyzing antitumor and antiviral actions of the murine IFNs in established animal models of disease." It is readily apparent from the last two sentences that Lawson applied the method of administering naked plasmid DNA encoding IFNs intramuscularly to established tumor models, i.e. mammals having tumors, which is equivalent to "a mammal with cancer" in the body of claim 1. Therefore, Lawson teaches administering to "a mammal with cancer" as claimed.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to inject a plasmid encoding a protein in a liposome intramuscularly

into a mouse as taught by Okamoto, wherein the plasmid encoded IFN-α as described by Lawson. One or ordinary skill in the art at the time the invention was made would have been motivated to replace the plasmid encoding MAGE-3 taught by Okamoto with the plasmid encoding IFN-α described by Lawson to determine the immune response to IFN-α in vivo. It also would have been obvious to one of ordinary skill in the art at the time the invention was made to inject a plasmid encoding INF-α into a mouse intramuscularly as taught by Lawson using an HVJ-liposome as described by Okamoto. One or ordinary skill in the art at the time the invention was made would have been motivated to add the HVJ-liposome described by Okamoto to the plasmid of Lawson because Okamoto taught HVJ-liposomes caused expression of the protein but plasmid alone did not (see abstract). One of ordinary skill in the art at the time the invention was made would have been motivated to use the plasmid of Lawson in the method of Okamoto because Lawson suggested using the plasmid in established models (pg 256, col. 1, lines 12-14).

Dependent claims 4-6 and 30-34 have been included because they further limit the phrase in the preamble and do not bear patentable weight.

Claims 46-49 are included because injecting the vector three times is equivalent to injecting the plasmid before, during or after gene therapy, i.e. the first injection is followed by gene therapy (the second and third injections), the second injection is preceded and followed by gene therapy (the first and third injection, etc.

Applicants' arguments summarize the teachings of Okamoto and Lawson and conclude that the combined teachings of Okamoto and Lawson fail to teach all the

limitations of claims. Applicants' argument is not persuasive because applicants have not pointed to one specific element that the combined teachings of Okamoto and Lawson fail to teach.

Applicants argue that one of ordinary skill would not have been motivated to combine Okamoto and Lawson because Lawson taught away from the combination. Applicants assert that one of skill would not have been motivated to cause a crush injury in order to treat cancer. Applicants argue Lawson teaches away from the claimed invention because Lawson taught only crush-injured mice developed a systemic IFN-α response. Applicants' arguments are not persuasive. The teachings of Lawson are not limited to injecting crush-injured muscle. Without evidence to the contrary, injecting non-injured muscle and obtaining ≤3.9 IU/ml IFN-α in the serum (pg 259, Table 4, "normal muscle) is equivalent to "administering into a non-injured muscle" and obtaining IFN-α expression "in an amount effective to treat said cancer" as claimed. Furthermore, Lawson specifically suggested administration of naked plasmid encoding IFNs into established tumor models (last two sentences of Lawson).

Conclusion

The prior art made of record and not relied upon remains pertinent to applicant's disclosure:

Horton (PNAS, Feb. 1999, Vol. 96, pg 1553-1558).

Manthorpe cited in the withdrawn obviousness type double patenting rejection (US Patent 6,875,748; Application No: 09/839,574, filed 4-23-01 and having priority to

11-28-00) was not available as prior art at the time the invention claimed in the instant application was made. The claimed invention in the instant application was at least taught in parent application 09/196,313, filed 11-20-98 to which applicants claim priority (see for example pg 59). Therefore, Manthorpe (effective filing date = 11-28-00) was not available as prior art at the time the invention claimed in the instant application was made (effective filing date is at least 11-20-98).

Wolff (US Patent 6,228,844) claims a method for stimulating vascular growth in the heart of a vertebrate, comprising injecting into the myocardium of the vertebrate a noninfectious, nonintegrating DNA construct comprising a promoter operably linked to a DNA sequence encoding vascular endothelial growth factor; wherein said DNA construct is injected in an amount sufficient that uptake of said DNA construct into cardiac cells of the vertebrate occurs, and sufficient expression of said vascular endothelial growth factor results, to stimulate vascular growth; and wherein said DNA construct is free from association with transfection-facilitating proteins, viral particles, liposomal formulations, charged lipids, and calcium phosphate precipitating agents. '844 suggested delivering interferons using DNA and delivering DNA to treat cancer. '844 did not teach IFN-α or obtaining expression levels of a protein in the serum that were capable of treating cancer by administering the DNA intramuscularly or into the peritoneal cavity as currently claimed.

Wolff (US Patent 6,706,694; Application No: 09/588,655) claims a method for delivering a physiologically active polypeptide to a vertebrate heart, comprising: administering in vivo into heart muscle of a vertebrate a composition comprising a DNA

operably encoding said physiologically active polypeptide through association with a promoter which directs synthesis of said polypeptide in vertebrate heart cells, and a pharmaceutically acceptable carrier; wherein said polynucleotide is free from association with liposomal formulations, charged lipids, transfection-facilitating precipitating agents, and transfection-facilitating viral particles; wherein a sufficient amount of said composition is administered to allow incorporation of said polynucleotide into heart cells of said vertebrate; and wherein said polypeptide is expressed in the heart of said vertebrate. '694 suggested delivering interferons using DNA and delivering DNA to treat cancer. '694 did not teach IFN-α or obtaining expression levels of a protein in the serum that were capable of treating cancer by administering the DNA intramuscularly or into the peritoneal cavity as currently claimed. It is not readily apparent that administering polynucleotides to the heart as in '694 can be used to treat cancer or metastasis as claimed in the instant application.

US Application number 10/028,782 has been considered for potential double patenting; however, '782 is limited to administering RNA which is patentably distinct from administering a DNA plasmid as claimed in the instant invention.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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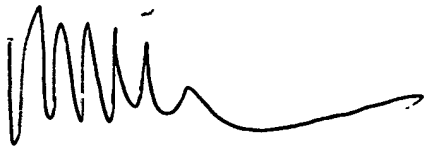
If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on 571-272-0735.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson



MICHAEL WILSON
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